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Magnesium Halide-Catalyzed Anti-Aldol Reactions of Chiral *N*-Acylthiazolidinethiones

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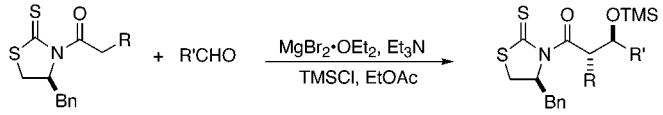
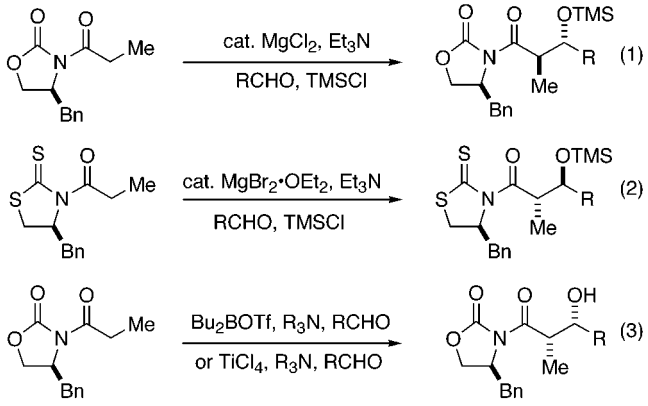
ABSTRACT



Diastereoselective direct aldol reactions of chiral *N*-acylthiazolidinethiones occur in high yield with preference for the illustrated anti diastereomer. This reaction is catalyzed by 10% $MgBr_2 \cdot OEt_2$ in the presence of triethylamine and chlorotrimethylsilane. Yields range from 56 to 93% with diastereoselectivity up to 19:1 for a variety of *N*-acylthiazolidinethiones and unsaturated aldehydes.

Ongoing efforts to further refine the aldol process have resulted in significant recent advances from a number of research groups.[1] In this context, we recently demonstrated that substoichiometric amounts of magnesium halides, in the presence of an amine base[2] and chlorotrimethylsilane (TMSCl), catalyze the direct aldol reaction of chiral *N*-acyloxazolidinones with high anti diastereoselectivity (eq 1).[3] This procedure substantially reduces the cost of the enolization process while affording access to a new auxiliary-based anti aldol process. In this Letter, we describe the extension of this methodology to chiral *N*-acylthiazolidinethiones (eq 2).[4] The realization of this goal, combined with our stoichiometric titanium- and boron-mediated aldol processes (eq 3),[5] now provides access to both syn and anti propionate aldol products of both absolute configurations.



Initial optimization studies focused on the Mg(II) source (Table 1). Aldol reactions with thiazolidinethione **1a**, cinnamaldehyde, triethylamine, and chlorotrimethylsilane in EtOAc identified $MgCl_2$ and $MgBr_2 \cdot OEt_2$ as likely metal

(1) (a) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466−2467 and references therein. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367−3368 and references therein. (c) Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497−2500.

(2) For a related soft-enolization procedure, see: Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985**, *50*, 4877−4879 and references therein.

(3) Evans, D. A.; Tedrow, J. S., Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393.

(4) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902 and references therein. (b) Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *49*, 1−36. (c) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418−1420.

(5) (a) Evans, D. A.; Bartroli, J.; Shih, T. L.; *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A., Rieger, D. L., Bilodeau, M. T., Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. (c) Evans, D. A., Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1−115. (d) Gage, J.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83−91.

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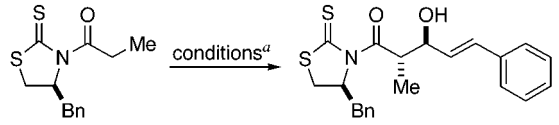
Table 1. Magnesium Sources for the Enolization Process

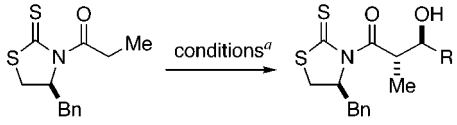


1a **2d**

entry	MgX_2	concn (**1a**)	convn (%)[b]	dr (%)[b,c]
1	$MgCl_2$	0.2 M	94	9:1
2	$MgCl_2$	0.4 M	94	10:1
3	$MgCl_2$	0.2 M	92	10:1
4	$MgBr_2{\cdot}OEt_2$	0.2 M	91	8:1
5	$MgBr_2{\cdot}OEt_2$	0.4 M	**99**	**10:1**
6	$MgBr_2{\cdot}OEt_2$	1.0 M	94	13:1
7	$Mg(NTf_2)_2$	0.2 M	87	5:1
8	$Mg(OTf)_2$	0.2 M	22	12:1
9	$Mg(ClO_4)_2$	0.2 M	64	4:1

[a] (1) MgX_2 (10 mol %), RCHO (1.1 equiv), Et_3N (2 equiv), TMSCl (1.1 equiv), EtOAc, 24 h; (2) 5:1 THF/1.0 N HCl. [b] Determined by 500 MHz ^1H NMR of the unpurified, silylated reaction mixture. [c] dr = diastereomeric ratio = (desired anti):(Σ other isomers).

Table 2. Addition of **1a** to Aldehydes (eq 2)



1a **2a-g**

entry	R	adduct	dr (%)[b,c]	yield (%)[d]
1	Ph	**2a**[e]	19:1	85
2	4-MeC_6H_4	**2b**[f]	19:1	92
3	4-$MeOC_6H_4$	**2c**[f]	19:1	91
4	CH=CHPh	**2d**[e]	10:1	87
5	$C(CH_3)$=CHPh	**2e**[e]	19:1	90
6	2-naphthyl	**2f**[e]	7:1	84
7	$C(CH_3)$=CH_2	**2g**[f]	7:1	56

[a] (1) $MgBr_2{\cdot}OEt_2$ (10 mol %), RCHO (1.1 equiv), Et_3N (2 equiv), TMSCl (1.5 equiv), 0.4 M in EtOAc, 24 h; (2) 5:1 THF/1.0 N HCl. [b] Determined by 500 MHz ^1H NMR of the unpurified, silylated reaction mixture. [c] dr = diastereomeric ratio = (desired anti):(Σ other isomers). [d] Isolated yield of major diastereomer. [e] Absolute configuration assigned by chemical correlation to known material. [f] Absolute configuration assigned by X-ray crystallography.

halide candidates. Other magnesium salts afforded aldol adducts in lower conversion or selectivity (diastereomer ratio (dr) = (desired anti):(Σ other isomers)). Upon varying the concentration of **1a**, $MgBr_2{\cdot}OEt_2$ emerged as the preferred catalyst.[6]

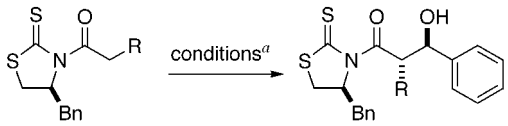
Examination of a number of trialkylamines clearly indicated triethylamine as the base of choice. While Hunig's base effected a selective reaction (7:1 dr), conversion declined (37%).[7] An increase in the amount of TMSCl (1.5 equiv) led to high conversion with no loss of diastereoselectivity.[8] We speculate that TMSCl may also be a scavenger of trace amounts of water in the solvent,[9] which was used without purification.

In the *N*-acyloxazolidinone system (eq 1), addition of substoichiometric amounts of $NaSbF_6$ sometimes afforded aldol adducts in higher conversion and selectivity.[3] Interestingly, this halide scavenger had little positive effect on the thiazolidinethione reaction; indeed, an increase in additive loading led to decreased selectivity and conversion.[10]

Addition of **1a** to various aldehydes was accomplished under the optimized reaction conditions (Table 2). Aromatic aldehydes (entries 1−3 and 6) afforded products with diastereoselectivity as high as 19:1 in excellent yield. Other unsaturated aldehydes also serve as viable substrates, although with diminished yield in the case of methacrolein (entries 4, 5, and 7). The major diastereomers were easily purified by chromatography. Recrystallization was possible for adducts **2b**, **2c**, and **2g**, allowing proof of absolute stereochemistry by X-ray crystallography. Each adduct, when cleaved from the auxiliary, was established to be antipodal to its corresponding oxazolidinone-derived adduct (eq 1).[3]

We next extended the reaction scope to thiazolidinethiones **1b**−**e**, synthesized in analogy to literature precedent.[4a,11] Each *N*-acylthiazolidinethione reacted smoothly with benzaldehyde in high yield and selectivity (Table 3). Some cases required higher catalyst loading to effect full conversion (entries 2 and 5).

Table 3. Addition of Representative *N*-Acylthiones



1a-e **2a,3b-e**

entry	R	adduct	dr (%)[b,c]	yield (%)[d]
1	CH_3	**2a**[e]	19:1	85
2	CH_2CH_3	**3b**[f]	10:1	88[g]
3	$CH_2CCH_2CH_2$	**3c**[f]	13:1	91
4	CH_2Ph	**3d**[h]	8:1	84
5	$CH_2CH(CH_3)_2$	**3e**[h]	19:1	93[i]

[a] (1) $MgBr_2{\cdot}OEt_2$ (10 mol %), PhCHO (1.1 equiv), Et_3N (2 equiv), TMSCl (1.5 equiv), 0.4 M in EtOAc, 24 h; (2) 5:1 THF/1.0 N HCl. [b] Determined by 500 MHz ^1H NMR of the unpurified, silylated reaction mixture. [c] dr = diastereomeric ratio = (desired anti):(Σ other isomers). [d] Isolated yield of major diastereomer. [e] Absolute configuration assigned by chemical correlation to known material. [f] Absolute configuration assigned by X-ray crystallography. [g] 20 mol % of $MgBr_2{\cdot}OEt_2$ was necessary to induce full conversion. [h] Absolute configuration assigned by analogy. [i] 15 mol % of $MgBr_2{\cdot}OEt_2$ was necessary to induce full conversion.

(6) Low conversion at high concentration may be due to poor solubility of some intermediates. White precipitate forms upon addition of amine base and persists throughout the reaction.

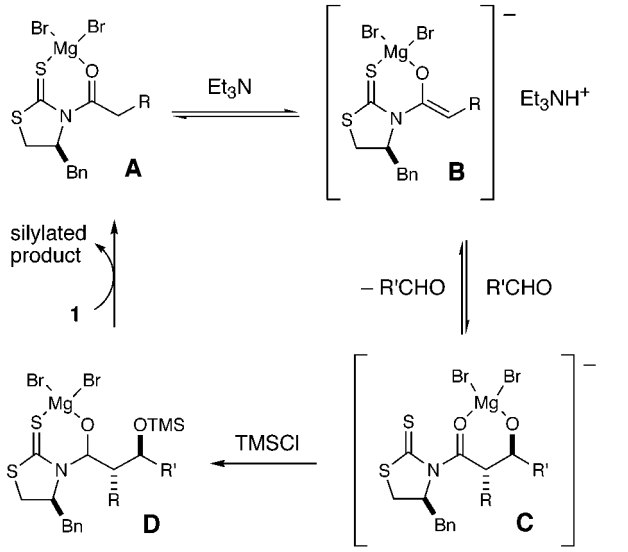
(7) Other bases (2,6-lutidine, *N*-methylmorpholine, imidazole) were inferior in terms of conversion or selectivity.

(8) Other silylating agents were less reactive (TESCl, conv = 0%) or selective (TMSBr, anti/syn = 4:1).

(9) Ethyl acetate, isopropyl acetate, dichloromethane, and acetonitrile were effective solvents in terms of conversion and selectivity. Ethyl acetate was selected for further studies.

(10) Addition of 13 mol % of $NaSbF_6$ to the reaction of **1a** and cinnamaldehyde: 90% y, dr = 90%. 25 mol % of $NaSbF_6$: 80% conv, dr = 82%. 46 mol % of $NaSbF_6$: 57% conv, dr = 83%.

Scheme 1. Proposed Catalytic Cycle

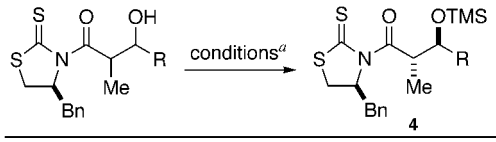


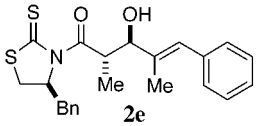
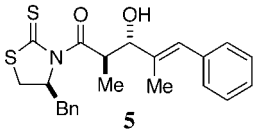
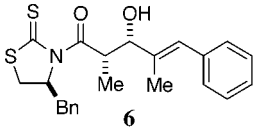
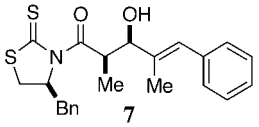
A proposed catalytic cycle is outlined in Scheme 1. Thiazolidinethione−magnesium complex **A** reacts with triethylamine, yielding magnesium enolate **B**, which adds reversibly[3] to the aldehyde, forming the magnesium aldolate **C**. Chlorotrimethylsilane then irreversibly traps this aldolate, which is subsequently displaced from the metal center by another molecule of *N*-acylthiazolidinethione.[12] *Because enolate silylation is not observed under the reaction conditions, a Mukaiyama-type pathway can be reasonably excluded.*

To test the reversibility of the carbon−carbon bond-forming step (**B** → **C**), a number of experiments were performed (Table 4). Diastereomerically pure (dr > 100:1) desilylated aldol adduct **2e** was subjected to the optimized reaction conditions (entry 1). After 24 h, ^{1}H NMR analysis showed that the minor anti diastereomer constituted 9% of the silylated product mixture. This result is consistent with a rapid retro-aldol cleavage of magnesium aldolate **C**, regenerating the aldehyde and magnesium enolate **B**. Selective reformation of **C**, followed by silylation, would produce a mixture of aldol adducts as observed. *Accordingly, the rate of retro-aldol cleavage appears to be faster than magnesium aldolate silylation.*

This conclusion is supported by the analogous equilibration experiment carried out with the minor anti aldol diastereomer **5**. A diasteromerically pure (dr > 100:1) sample of **5** was isomerized to a 7:1 mixture of **2e**:**5** (entry 2). Even the independently synthesized[4a,b] syn adduct **6** could be converted to **4** in good yield (entry 3).[13] Finally, syn aldol adduct **7** did not interconvert cleanly to the principal anti adduct **4** (entry 4), suggesting that the rates of silylation and retro-aldol cleavage might be competitive with this aldol diastereomer. In conclusion, while these experiments document the reversibility of some of the steps, they by no means establish that reaction diastereoselection is operating under thermodynamic control.

Table 4. Isomerization Experiments



entry	initial isomer	dr(%)[b]
1	 **2e**	9:1
2	 **5**	7:1
3	 **6**	16:1
4	 **7**	1.5:1[c]

[a] (1) $MgBr_2 \cdot OEt_2$ (10 mol %), Et_3N (2 equiv), TMSCl (1.5 equiv), 0.4 M in EtOAc, 24 h. [b] Determined by 500 MHz ^{1}H NMR of the unpurified, silylated reaction mixture. dr = diastereomeric ratio = (desired anti):(Σ other isomers). [c] Anti/syn = 77:23.

The mechanistic intricacies of these reactions are noteworthy. This reaction presents two stereochemical issues: enolate diastereoface selectivity and anti aldol diastereoselection. On the basis of the weight of circumstantial evidence, all enolization procedures to date to form boron, titanium, lithium, or sodium enolates with this family of imides implicate the intervention of (*Z*) metal enolates. Given the assumption that this is the geometry of the intervening enolate, the enolate face selectivity observed for the *N*-acyloxazolidinone-derived magnesium enolate is fully consistent with a chelate-controlled process (eq 4) as is observed in analogous metal enolate alkylation and Michael addition reactions.[14] *In contrast, the N-acylthiazolidinethione-derived magnesium enolates exhibit the opposite face selection in these reactions*. This observation negates the possibility that the thione C═S moiety is coordinating to the Mg center during the aldol transition state. Rather, enolate face selection derived from the minimization of C═O↔C═S dipole interactions provides the stereocontrol on the enolate reaction partner (eq 5) as is observed for the analogous boron aldol reactions.[5a]

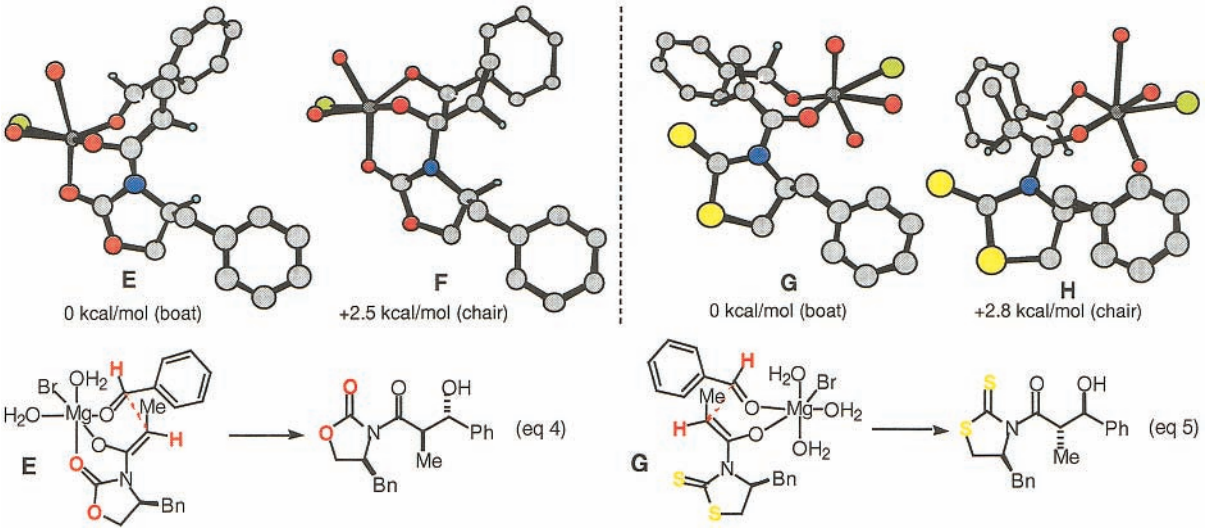
(11) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604−6607.

(12) Silylated adducts are configurationally stable under the reaction conditions.

(13) Further experiments to eliminate epimerization as a source of isomerization have been conducted and will be reported in due course.

(14) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739. (b) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453.

Scheme 2. PM3 Calculations Suggest the Invervention of a Boat Transition State



Since these aldol addition reactions afford the unexpected anti aldol product from the (*Z*) metal enolate, the intervention of a chair Zimmerman−Traxler transition state is precluded. On this basis we wish to suggest that these reactions are proceeding via either five- or six-coordinate Mg coordination geometries where the boat-metal transition structures such as **E**−**H** (Scheme 2**)** are reasonable.[15] Semiempirical calculations (PM3) support the premise that a twist-boat conformation should be favored for the magnesium aldol transition state when the length of the forming carbon−carbon bond is constrained to 2.0 Å.[16] Chair **F** is 2.5 kcal/mol higher in energy than boat **E**; chair **H** is 2.8 kcal/mol higher in energy than boat **G**.[17] Thus, judicious auxiliary choice controls the enolate face-selectivity of the magnesium aldol, allowing access to either anti diastereomer.

In conclusion, $MgBr_2 \cdot OEt_2$ selectively catalyzes the direct aldol of *N*-acylthiazolidinethiones. The anti propionate adducts are complementary to adducts derived from *N*-acyloxazolidinones. Investigations continue into the mechanism, diastereoselectivity, and potential enantioselectivity of this reaction.

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Supporting Information Available: Experimental procedures for all new compounds as well as calculation procedures and X-ray crystallographic data for **2b**, **2c**, **2g**, **3b**, and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For the sake of space, we have not presented the analogous five-coordinate Mg transition states. We speculate that the O−Mg−O═C bond angle in these complexes will also be ∼90° with the O═C (RCHO) ligand oriented in the equatorial plane and the O-enolate ligand in axial position to optimize the electronic effects conferred on the reaction partners by the metal center.

(16) Li, Y.; Paddon-Row: M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493.

(17) Transition-structure optimizations were performed at the PM3 level using the Spartan Semiempirical Program 5.0 (Wavefunction Inc., Irvine, CA 92715) on a Silicon Graphics Impact 10000 (195 MHz, 128 M RAM) running IRIX 6.2. Calculations were performed without solvent using these parameters: optcycle = 2000, maxcycle = 2000, charge = 0, multiplicity = 0. Calculations converged (energy difference between cycles <0.0005 kcal/mol) in ≤ 4 h CPU time.